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Application No. 10/072,823	Filing Date February 8, 2002	Examiner Meller	Group Art Unit 1655

Invention: ANTI-CANCER AGENTS AND METHOD OF USE THEREOF

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TRANSMITTAL LETTER (General - Patent Pending)	Docket No. NOV-0001

In Re Application Of: Chen

Application No.	Filing Date	Examiner	Customer No.	Group Art Unit	Confirmation No.
10/072,823	February 8, 2002	Meller	23413	1655	1435

Title: ANTI-CANCER AGENTS AND METHOD OF USE THEREOF

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Reply Brief (12 pages)

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Karen A. LeCuyer
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P16A/REV03

Docket No. NOV-0001

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT:	CHEN	) Before the Board of Appeals
SERIAL NUMBER:	10/072,823	)
FILED:	February 8, 2002	) Appeal No.:
FOR:	ANTI-CANCER AGENTS AND METHOD OF USE THEREOF	)

REPLY BRIEF

I. REAL PARTY IN INTEREST

The real party in interest in this appeal is Sophie Chen.

II. RELATED APPEALS AND INTERFERENCES

There are no other appeals or interferences known to Appellant, Appellant's legal representatives, or assignee which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

III. STATUS OF THE CLAIMS

Claims 1-9, 11-16, 18-23, 26-29, and 32-35 are pending in the application. All of the pending claims stand rejected. The rejection of claims 1-9, 11-16, 18-23, 26-29, and 32-35 is appealed.

IV. STATUS OF AMENDMENTS

There have been no amendments filed subsequent to receipt of the Final Office Action dated July 28, 2004.

V. SUMMARY OF THE INVENTION

The present invention relates to compositions suitable for treatment of cancer such as prostate, breast, colon, lung, and bladder cancers. (In dependent claim 1 is directed to a composition for treating or preventing prostate cancer or breast cancer (page 6, lines 3-4) comprising oridonin, a pharmaceutically acceptable salt or ester of oridonin, a selectively substituted analog of oridonin, or a combination thereof (Page 7, lines 1-12); and lupulone, a pharmaceutically acceptable salt or ester of lupulone, a selectively substituted analog of lupulone, or a combination thereof (Page 7, line 13-Page 8 line 9); wherein the composition is suitable for the treatment or prevention of prostate cancer or breast cancer.

The compositions comprise compounds from various plant sources that may be extracts found naturally in the plant, or that may be synthesized and/or altered by pharmaceutical means. (Page 6, lines 5-7) The extracts include compounds such as oridonin, lupulone, bavachin,

bavachalcone, bavachinin, bavachromene, genscnoside, baicalin, soy flavonoid, soy isoflavonoid, curcumin, pharmaccutically acceptable salts or esters, selectively substituted analogs, and combinations comprising at least one of the foregoing compounds. (Page 6, lines 12-16) Administration of compounds such as oridonin, lupulone, bavachin, bavachalcone, bavachinin, and bavachromene is effective to have anti-prostate cancer, anti-breast cancer, anti-colon cancer, anti-lung cancer, or anti-bladder cancer activity *in vivo*. (Page 11, lines 4-10) The compounds and/or plant extracts may be formulated as pharmaceutically acceptable compositions.

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

Claims 1-9, 11-16, 18-23, 26-29, and 32-35 stand rejected under 35 U.S.C. § 103 as being allegedly unpatentable over JP 57-167938, GB 1476016, or JP 352102434 taken with JP 11-236334 or JP 52-145509.

VII. ARGUMENT

A. Claims 1-9, 11-16, 18-23, 26-29, and 32-35 are Patentable Under 35 U.S.C. § 103 Over JP 57-167938, GB 1476016, or JP 352102434 Taken With JP 11-236334 or JP 52-145509.

In the Examiner's Answer of February 16, 2006, the Examiner states that "Since the [references?] clearly show that individually the in the prior art of record lupulone and oridonin are used to treat cancer then it would have been obvious to combine lupulone and oridonin together to make a third composition to treat cancer". (Examiner's Answer, page 5) Applicants maintain that the Examiner has greatly underestimated the complexity of cancer treatment. Based on the mere suggestion of anti-cancer activity of two agents, one of skill in the art would not combine them to treat a particular form of cancer. Further there is no expectation of success for such a combination which is merely obvious to try.

For an obviousness rejection to be proper, the Examiner must meet the burden of establishing that all elements of the invention are disclosed in the prior art; that the prior art relied upon, coupled with knowledge generally available in the art at the time of the invention,

must contain some suggestion or incentive that would have motivated the skilled artisan to modify a reference or combined references; and that the proposed modification of the prior art must have had a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was make. *In re Fine*, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988); *Amgen v. Chugai Pharmaceuticals Co.*, 927 U.S.P.Q.2d, 1016, 1023 (Fed. Cir. 1996).

A finding of "obvious to try" does not provide the proper showing for an obviousness determination. The requirement for a determination of obviousness is that "both the suggestion and the expectation of success must be founded in the prior art, not in applicant's disclosure" (emphasis added). *In re Dow Chem.*, 837 F.2d 469, 473, 5 U.S.P.Q.2d 1529, 1531 (Fed. Cir. 1988). An Examiner, then, cannot base a determination of obviousness on what the skilled person in the art might try or find obvious to try. Rather, the proper test requires determining what the prior art would have led the skilled person to do.

In a complex field such as cancer therapy, the mere suggestion of anti-cancer activity in a compound is not sufficient to motivate one of skill in the art to make a particular combination, absent information as to the mechanism of action of the components. Further, there is no expectation of success for such a combination.

Cancer is a complex disease having many different molecular mechanisms. In fact, as known to those of skill in the art, cancer is not one disease but many diseases having non-overlapping molecular mechanisms. As stated in Golub, "Effective treatment for cancer requires not only the discovery of drugs with antitumor activity, but also knowledge of the best way to combine these drugs." (EXHIBIT 3, May 7, 2004 amendment, Mining the genome for combination therapies) Previous combinations for the treatment of lymphoblastic leukemia as described in Golub had been discovered by "clinical empiricism and trial and error". This is the standard for obvious to try. While it may be obvious to try combinations of compound having antitumor activity to treat a particular cancer, there is no expectation of success for such a combination.

As further described in Golub, combination treatment of lymphoblastic leukemia was advanced by "molecular insights" into leukemia therapy. As to the future of combination cancer

therapy, it is stated "combination approaches will remain critical- either simultaneous targeting of a single pathway so as to avoid drug resistance, or targeting of two or more pathways, each of which is essential for tumor cell survival".

The Examiner has dismissed the Golub reference stating that because this reference does not address the appellant's invention, it adds nothing to the appellant's arguments. (Examiner's Answer, page 6) Appellant strongly disagrees. This reference is a review article in Nature Medicine, a highly respected journal. This news and views article speaks generally about the state of the art of combination therapy for cancer treatment. This article is relevant to the present discussion, because it clearly shows that one of skill in the art, when treating a particular cancer, would not combine at random two agents having antitumor properties with any expectation of success. This reference highlights the Examiner's oversimplification of the disease of cancer and illustrates the state of the art of combination therapy in this field.

The Examiner has also stated that "all that is required is that there is a clear motivation to combine the two ingredients together (lupulone and oridonin) to create a third composition which has the same purpose as the two ingredients, which is true". (Examiner's Answer, page 6) Appellants strongly disagree with the Examiner. What is required is the motivation to combine, as well as an expectation of success. In this case, there is no motivation to combine and no expectation of success for the combination of lupulone and oridonin.

There is no motivation to combine or expectation of success for the combination of two anti-cancer agent, absent some suggestion that the two agents are compatible. In this case, the references provide no teaching that these two agents are in any way compatible. As explained previously, combinations of anti-cancer agents can in fact have negative effects. For example, antimitotic agents such as paclitaxel and G_1-S arresting agents such as 5-fluorouracil have antagonistic effects. (Johnson et al. Clinical Cancer Research 5, 2559-2565, 1999, EXBIBIT 4, May 7, 2004 amendment) The references provided by the Examiner provide no suggestion as to the mechanism of action of lupulone and oridonin. Based on the state of the art in the field of

anti-cancer agents and the references cited, there is no motivation to combine and no expectation of success for this combination.

In the present case, the Appellant's application and not the cited references has provided ample support for the use of a combination of oridonin and lupulone to treat breast and prostate cancer. As shown in the Examples of the present application, oridonin affects the cell cycle of LNCAP androgen receptor positive prostate cancer cells at the G1 phase; it affects the cell cycle of DU-145 androgen receptor negative cells at the G2M phase; and it affects the cell cycle of MCF-7 breast cancer cells at the S phase. Lupulone affects the cell cycle of LNCAP androgen receptor positive prostate cancer cells at the G2M phase and induces a strong apoptosis; and it affects the cell cycle of MCF-7 breast cancer cells at the G1 phase. It was further shown in the present application that oridonin down-regulates Bcl-2 and up-regulates Bax and p53, which ultimately leads to an apoptotic cascade in the cancer cells. As such, both oridonin and lupulone complement each other in inducing apoptosis of the targeted cancer cells at various cell cycle stages. Absent data such as that provided by the Appellant's application, one of skill in the art would have no motivation to combine lupulone and oridonin and no expectation of success for the combination.

In summary, Appellant has clearly shown that oridonin and lupulone an be used to treat breast and prostate cancer. In addition, because oridonin and lupulone are both cell cycle inhibitors, they are not expected to have antagonistic effects. The cited references provide neither the motivation nor the expectation of success for this combination. Appellant submits that the present claims are patentable over the prior art.

B. Conclusion

In view of the foregoing, it is urged that the final rejection of Claims 1-9, 11-16, 18-23, 26-29, and 32-35 be overturned and the Claims allowed. The final rejection is in error and should be reversed.

If there are any additional charges with respect to this Brief, please charge them to Deposit Account No. 06-1130.

Respectfully submitted,

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VIII. CLAIMS APPENDIX

1. A composition for treating or preventing prostate cancer or breast cancer:

oridonin, a pharmaceutically acceptable salt or ester of oridonin, a selectively substituted analog of oridonin, or a combination thereof; and

lupulone, a pharmaceutically acceptable salt or ester of lupulone, a selectively substituted analog of lupulone, or a combination thereof;

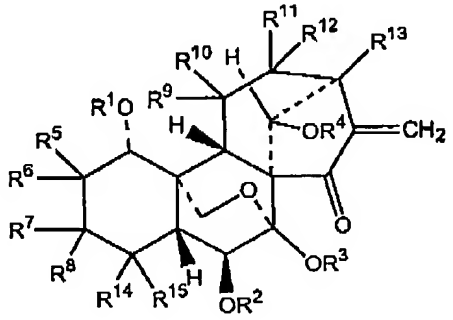
wherein the composition is suitable for the treatment or prevention of prostate cancer or breast cancer.

2. The composition of Claim 1, in an ingestible form.

3. The composition of Claim 2, wherein the ingestible form is a powder, a capsule, or a tablet.

4. The composition of Claim 1, in the form of a suppository.

5. The composition of Claim 1, comprising a compound having the structure



wherein R^1-R^4 are each independently hydrogen, C_1-C_6 alkyl, or C_1-C_{12} acyl, R^5-R^{13} are each independently hydrogen or C_1-C_6 alkyl, and R^{14} and R^{15} are each independently C_1-C_6 alkyl, with the proviso that at least 4 of R^5-R^{13} are hydrogen.

6. The composition of Claim 5, wherein R^1-R^4 are each independently hydrogen, methyl, ethyl, acetyl, or propionyl.

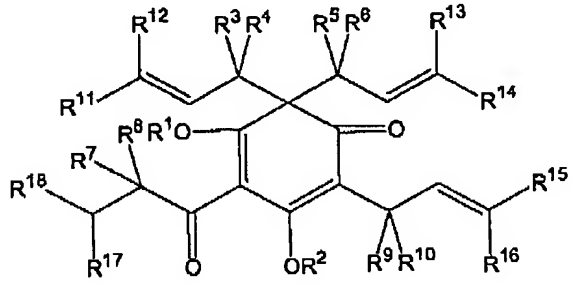
7. The composition of Claim 5, wherein R^5-R^{13} are each independently hydrogen, methyl, or ethyl.

8. The composition of Claim 5, wherein R^1-R^{13} are hydrogen, and R^{14} and R^{15} are methyl.

9. The composition of Claim 5, comprising an extract of Rabdosia rubescens.

10. (canceled)

11. The composition of Claim 1, comprising a compound having the structure



wherein R^1 and R^2 are each independently hydrogen, C_1-C_6 alkyl, or C_1-C_{12} acyl; R^3-R^{10} are each independently hydrogen or C_1-C_6 alkyl with the proviso that at least four of R^3-R^{10} are hydrogen; and R^{11}-R^{18} are each independently C_1-C_6 alkyl.

12. The composition of Claim 11, wherein R^1 and R^2 are each independently hydrogen, methyl, ethyl, acetyl, or propionyl.

13. The composition of Claim 11, wherein R^3-R^{10} are each independently hydrogen, methyl, or ethyl.

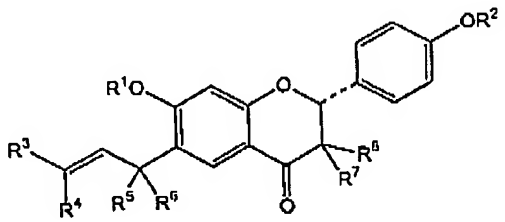
14. The composition of Claim 11, wherein R^{11}-R^{18} are each independently methyl or ethyl.

15. The composition of Claim 11, wherein R^1-R^{10} are each hydrogen, and R^{11}-R^{18} are each methyl.

16. The composition of Claim 11, comprising an extract of Humulus lupulus.

17. (canceled)

18. The composition of Claim 1, comprising a compound having the structure



wherein R^1 and R^2 are each independently hydrogen, C_1-C_6 alkyl, or C_1-C_{12} acyl; and R^3-R^8 are each independently hydrogen or C_1-C_6 alkyl with the proviso that at least two of R^3-R^8 are hydrogen.

19. The composition of Claim 18, wherein R^1 and R^2 are each independently hydrogen, methyl, ethyl, acetyl, or propionyl.

20. The composition of Claim 18, wherein R^3-R^8 are each independently hydrogen, methyl, or ethyl.

21. The composition of Claim 18, wherein R^3 and R^4 are methyl.

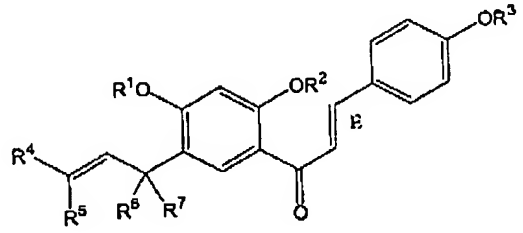
22. The composition of Claim 18, wherein R^1, R^2, and R^5-R^8 are hydrogen; and R^3 and R^4 are methyl.

23. The composition of Claim 18, wherein R^2 and R^5-R^8 are hydrogen; and R^1, R^3, and R^4 are methyl.

24. (canceled)

25. (canceled)

26. The composition of Claim 1, comprising a compound having the formula



wherein R^1-R^3 are each independently hydrogen, C_1-C_6 alkyl, or C_1-C_{12} acyl; and R^4-R^7 are each independently hydrogen or C_1-C_6 alkyl.

27. The composition of Claim 26, wherein R^1-R^3 are each independently hydrogen, methyl, ethyl, acetyl, or propionyl.

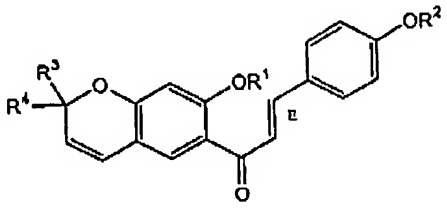
28. The composition of Claim 26, wherein R^4-R^7 are each independently hydrogen, methyl, or ethyl.

29. The composition of Claim 26, wherein R^1-R^3, R^6, and R^7 are hydrogen; and R^4 and R^5 are methyl.

30. (canceled)

31. (canceled)

32. The composition of Claim 1, comprising a compound having the structure



wherein R^1 and R^2 are each independently hydrogen, C_1-C_6 alkyl, or C_1-C_{12} acyl; and R^3 and R^4 are each independently hydrogen or C_1-C_6 alkyl.

33. The composition of Claim 32, wherein R^1 and R^2 are each independently hydrogen, methyl, ethyl, acetyl, or propionyl.

34. The composition of Claim 32, wherein R^3 and R^4 are each independently hydrogen, methyl, or ethyl.

35. The composition of Claim 32, wherein R^1 and R^2 are hydrogen; and R^3 and R^4 are methyl.

36-48. (canceled)

IX. EVIDENCE APPENDIX

There is no evidence submitted pursuant to 37 C.F.R. §1.130, 37 C.F.R. §1.131, or 37 C.F.R. §1.132 or any other evidence entered by the Examiner and relied upon by the Appellant in this appeal, known to the Appellants, Appellants' legal representatives, or assignee.

X. RELATED PROCEEDING APPENDIX

There are no other related appeals or interferences known to Appellants, Appellants' legal representatives, or assignee that will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.